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# DISCUSSION ON THE SERUM TREATMENT OF SCARLET FEVER.

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## Dr. R. A. O'BRIEN.

As my own clinical opportunities are limited, I recently referred the three important questions before us to the superintendents of three hospitals—all outside London—because I anticipated that experienced London clinicians would be present at this meeting and also because the disease in the north has probably been of a more severe type than the very mild type commonly seen in London. The three superintendents generously gave me permission to quote their opinions and experience this evening.

In the *Edinburgh Medical Journal*, December, 1926, Dr. Benson, of the City Hospital, Edinburgh, described his results in the treatment of 100 cases of scarlet fever. He concludes that: "The administration of antitoxic serum within the first forty-eight hours of the disease has a very favourable influence on the specific toxæmia of scarlet fever. In relieving the more urgent symptoms of the acute stage it undoubtedly renders the patient more comfortable.

"There are indications that the liability to subsequent complications is diminished.

"The administration of serum even on the first day of illness apparently does not act as an absolute safeguard against the subsequent development of complications of septic type in convalescence.

"In toxic cases of scarlet fever, serum should be administered either intravenously or intramuscularly at the earliest opportunity and the dose repeated if necessary."

Dr. Benson has since treated between two and three hundred patients with English concentrated serum. The dose was usually 10 c.c.—exceptionally 20 c.c. He says: "The former dose exercises a definitely favourable effect in the mild and moderate cases. The serum does not seem to touch the septic type of the disease. Serum rashes were troublesome. Serum therapy is certainly worth while, more particularly in the sharper cases. I am not, however, prepared to discharge my patients in the third week of convalescence merely on the strength of serum treatment."

Dr. Harries, of the City Hospital, Birmingham, writes: "We have used scarlet fever antitoxin for about eighteen months, and concentrated antitoxin as a routine in all except the mildest cases for six to eight months. Serum sickness is infrequent and trifling when it occurs. A dose of 10 c.c. is sufficient in the average case.

"There is some reason for hoping that serum will diminish complications and will reduce the necessary stay in hospital. If it has these effects, it is obvious that the money spent on antitoxin would be well spent.

"It is unnecessary to reiterate the well-known effects of scarlet fever antitoxin on the toxæmia of scarlet fever. The more striking the case the more striking are the results of treatment with scarlet fever antitoxin. The problem of scarlet fever is, in my opinion, one of late morbidity, and it is impossible to forecast what complications a patient with a mild initial attack may develop in the second or third

week. Only a long series of cases treated and untreated with serum can establish whether serum treatment does decrease the incidence of late complications.

"I found no direct curative influence on the septic complications of scarlet fever. A serum on the market, stated to be antibacterial as well as antitoxic, has, in my hands, given no antibacterial results.

"To sum up, I have no personal doubt as to the curative value of scarlet fever antitoxin, and should regard it as a failure of my duty if I withheld antitoxin from a severe case of scarlet fever.

"With regard to prophylaxis, we have never yet known a child who has been rendered Dick-negative by antitoxin to contract scarlet fever, although repeatedly exposed. We have, however, seen children, whose passive immunity had waned and who had become Dick-positive, contract scarlet fever after exposure."

Dr. Harries in a later letter adds that in fifty successive patients treated with concentrated serum there were no septic complications. Thirty-three patients showed no symptoms of serum sickness ; amongst those with symptoms none were in any way severe, and all the patients were ready for discharge in thirty days. At present all clinically severe cases receive serum ; of the others every alternate patient receives serum.

Dr. Rundle (Liverpool City Hospital) has used serum in about one hundred cases. Five deaths occurred. "The cases were selected for treatment by reason of their 'toxicity,' and many of them would, in our opinion, have succumbed without the serum. The hundred cases includes, however, about twenty-five of the septic variety, coming late under treatment and deriving no obvious benefit from the antitoxin. The deaths, with one exception, occurred amongst this 'septic' type. Antitoxin is of no use once septic throat, adenitis, etc., have set in. The serum phenomena have been more intense than one finds with antidiphtheria serum. Although one expects a dramatic fall of temperature and general alleviation with serum in the toxic cases, there is no guarantee that the usual complications will not arise. We have had some severe suppurative conditions in patients who had serum some days previously."

The experiences of these three observers apparently agree fairly closely with the general experience of clinicians in America.

The question of specificity and standardization of scarlet fever antitoxin arises directly from the important question of dose raised by Dr. Goodall. My colleagues, Dr. Parish and Dr. Okell, have kindly allowed me to show two tables from a paper which they have in preparation. From the first table it will be seen that when a sufficient dose of culture of the hæmolytic streptococcus of scarlet fever is injected intravenously into a rabbit, the rabbit almost invariably dies of the initial "toxæmia" or "septicæmia" in less than two days. Normal horse serum and non-specific antitoxin do not protect the rabbits, human convalescent serum does so to some extent ; concentrated scarlet fever serum protects completely when given in a moderate dose. The most interesting part of the table is that relating to the use of the serum that has been issued commercially by many laboratories for many years past as antistreptococcus scarlet fever antiserum. This serum was a legacy from the period about 1902 when Marmorek, Gabritchewsky, Moser, Schick and others used the serum of horses injected with broth culture of streptococci obtained from the throats of scarlet fever patients for the treatment of scarlet fever. There is very little doubt, from their clinical records, that the serum they used at first had a definite therapeutic effect on scarlet fever. The serum later slowly somewhat declined in favour because some workers failed to record any improvement in their patients after the use of the serum, and further, using large doses of the serum, they found that their patients often had severe serum reactions. The

incidence of these serum reactions to-day has been greatly reduced by the well-known processes of concentration. Examination of some of the serum made by this method has shown that it has a definite but low amount of antitoxin in it.

Dr. Parish and Dr. Okell have shown that some of this serum was approximately half as strong as a high value concentrated scarlet fever antitoxin of to-day. Unfortunately, it does not seem to have occurred to anyone to use an obviously simple method of titrating this serum, i.e., to find accurately how much of this serum was necessary to protect from scarlet fever contacts exposed to infection. Had this been done, it is fairly certain that some of the serum in use could easily have been demonstrated to contain a very small amount of antitoxin and would have been replaced by the most potent serum then available.

The second table relates to some very recent work. A fascinating immunological puzzle concerns the relation of the hæmolytic streptococci to one another. The hæmolytic streptococcus of follicular tonsillitis and that of puerperal septicæmia cannot with any certainty be distinguished by the bacteriologist from the streptococci found in every scarlet fever throat. An obvious method of attack on this problem is to make toxins from the various organisms and test them on human beings, to see if the same patients are positive to all three toxins or negative to all three toxins. And, if so, to discover whether the positive Dick reaction is neutralized by anti-follicular tonsillitis antoxin or by anti-puerperal, anti-cellulitis, or other antitoxin.

Such a research has long been projected by Dr. Okell, and, as opportunity offers, is being carried through. But while waiting for the results of tests on human beings, Dr. Parish and Dr. Okell have carried out in rabbits the experiment indicated. It is remarkable that six strains of hæmolytic streptococci from patients suffering from puerperal septicæmia and two strains from patients with follicular tonsillitis, which promptly kill all the unprotected rabbits, fail to kill within three days any of the rabbits protected with scarlet fever concentrated antitoxin. The antigenic overlap amongst these hæmolytic streptococci must be very close, amounting perhaps to identity. It is reasonable to hope from these results that the homologous antitoxins, and also the concentrated scarlet fever antitoxin, may be of definite service in combating at least the first toxæmia or septicæmia of follicular tonsillitis, puerperal septicæmia and cellulitis, etc., caused by this same group of hæmolytic streptococci.

The question of *dosage* is closely linked with that of standardization. The various methods are well known, i.e., neutralization of toxin in the skin of human beings by measured quantities of antitoxin, similarly in goats, the determination of an adequate dose for passive immunity, the dose necessary for Schultz-Charlton blanching, and the rabbit protective dose. The determination of the prophylactic dose, i.e., one that will turn positive Dick reactors negative overnight and keep them negative during the incubation period of scarlet fever, has proved to be easy and supplies a method available in the hands of the hospital superintendent for titrating the serum he proposes to use, should he so desire. It is found that, with a good concentrated serum, this dose varies from 2 c.c. to 4 c.c. or 5 c.c. Such a serum will usually produce blanching when injected into an early scarlet fever rash in a dilution of upwards of $\frac{1}{4000}$.

## Conclusions.

Concentrated scarlet fever antitoxin is of use in the treatment of scarlet fever. No antitoxin or other serum at present available has any direct action on septic complications. The early use of serum probably reduces the liability to late septic complications and reduces the length of stay in hospital, but many further observations are required.

Concentrated scarlet fever antitoxin protects rabbits against the first "toxæmia" or "septicæmia" caused by hæmolytic streptococci obtained from cases of follicular tonsillitis, puerperal fever, cellulitis, etc. The antigens of these various cultures must bear a close relationship to each other.

TABLE I (PARISH AND OKELL).—RABBITS INJECTED INTRAVENOUSLY WITH 10 C.C. OF A TWENTY-HOUR DIGEST BROTH CULTURE OF SCARLET FEVER STREPTOCOCCUS. SERUM INJECTED INTRAVENOUSLY FOUR TO SIX HOURS PRIOR TO INJECTION OF CULTURE.

| | Total rabbits | Percentage living six days after injection of culture. 5 c.c. or more | 1·0 c.c. | 0·25 c.c. | 0·1 c.c. |
|---|---|---|---|---|---|
| Normal horse serum ... ... } Concentrated diphtheria antitoxin } ... ... ... | 20 | 5 | — | — | — |
| Unconcentrated anti-streptococcus serum erysipelas ... | | | | | |
| ,, ,, ,, strangles ... | | | | | |
| ,, ,, ,, measles ... | 29 | 17 | — | — | — |
| ,, ,, ,, puerperal ... | | | | | |
| ,, ,, ,, pyogenes (Swann) | | | | | |
| ,, ,, ,, ,, (Shilling) | 17 | 29 | 0 | — | — |
| ,, ,, ,, S[1] ... ... | 6 | 50 | — | — | — |
| Serum from scarlet fever convalescents (Dick-negative) ... | 6 | 50 | — | — | — |
| Unconcentrated scarlet fever antitoxin (early stage of immunization), batch "P" ... ... ... ... | 9 | 66 | 0 | — | — |
| Unconcentrated scarlet fever antitoxin (late stage of immunization), batch "Q" ... ... ... ... ... | 15 | 77 | 33 | 0 | — |
| Concentrated scarlet fever antitoxin, batch "R" ... ... | 15 | 88 | 66 | 33 | — |
| ,, ,, ,, ,, "S" ... ... | 12 | 100 | 100 | 66 | 33 |

TABLE II (PARISH AND OKELL).—RABBITS INJECTED WITH SERUM INTRAVENOUSLY FOUR TO SIX HOURS BEFORE INJECTION OF CULTURE INTRAVENOUSLY.

| | Unprotected | Protected Streptococcus antitoxic serum | | | | |
|---|---|---|---|---|---|---|
| Culture, 5 to 20 c.c. | Total number of rabbits | No serum or normal horse serum or concentrated diphtheria serum | Concentrated scarlet fever, 5 c.c. | Concentrated puerperal, 5 c.c. | Unconcentrated pyogenes, 10 to 15 c.c. | Unconcentrated erysipelas, 10-15 c.c |
| Tonsillitis ... ... | 24 | 0 | 77 | — | 33 | — |
| ,, ... ... | 9 | 0 | 100 | — | 33 | — |
| Lymphangitis ... | 9 | 0 | 100 | — | 66 | — |
| Fatal septicæmia ... | 12 | 0 | 33 | — | 66 | — |
| Severe septicæmia ... | 15 | 0 | 66 | — | — | — |
| Endocarditis ... | 12 | 0 | 83 | — | — | — |
| Puerperal fever (uterus) ... | 25 | 10 | 83 | 16 | 0 (conc., 5 c.c.) | — |
| ,, ,, ... | 25 | | 100 | 50 | 33 (conc., 5 c.c.) | — |
| ,, (blood) ... | 11 | 0 | 100 | 100 | — | — |
| ,, ,, ... | 9 | 33 | 66 | 66 | — | — |
| ,, (uterus) ... | 11 | 0 | 100 | 33 | — | — |
| ,, (blood) ... | 11 | 0 | 100 | 33 | — | — |
| Erysipelas ... ... | 36 | 8 | 70 (conc., 5 to 15 c.c.) | — | — | 77 |

## Dr. H. J. PARISH

said that further experiments carried out by Dr. Okell and himself appeared to suggest the identity of hæmolytic streptococcal toxins. Rabbits could be killed by the intravenous injection, not only of scarlet fever streptococci, as mentioned by Dr. O'Brien, but also of toxin; large doses of toxin, however—(20 to 40 c.c.)—were required to ensure deaths overnight. If antitoxin were given from four to six hours before injecting the toxin, the rabbits survived. Such experiments had only been possible with scarlet fever toxin, as erysipelas and puerperal fever toxins tended to be much weaker, and there was a limit to the volume of toxin broth one could inject into the rabbit's circulation.

Yesterday he (the speaker) had injected three Dick-positive and two Dick-negative individuals with 1 in 1,000 scarlet fever and 1 in 250 erysipelas and puerperal fever toxins. In each Dick-positive individual the scarlet fever toxin gave the best reaction, the puerperal next, and the erysipelas least. In the Dick-negative persons no reactions occurred with any of the toxins. These experiments on rabbits and in man suggested only quantitative differences between the three toxins.

To parallel the failure of antitoxin to prevent the septic complications of scarlet fever : large amounts of serum did not prevent the development of arthritis in rabbits injected with cultures of hæmolytic streptococci. In practically all the rabbits which were protected against the initial phases of the infection, joint lesions developed at the end of the first week. At first these were slight, but later became very severe ; there was usually pus in the joints and neighbouring muscles from which one could recover hæmolytic streptococci.

## Dr. O'Brien (in reply)

said that Dr. Caiger's account of results obtained by the use of serum some years ago made him (the speaker) feel that he had failed to make his point of reconciling what had been done in the past with what was known to-day. The anti-streptococcus serum which had been made for twenty years past apparently protected 50 per cent. of rabbits in the Parish-Okell test. It was practically certain that the serum Moser used contained antitoxin. None of that was available now, but one could test the material made a few years ago. The Dick serum had been first made in April, 1924, but we had to-day a serum made before that date, by the old methods of Moser and others, and this serum clearly protected rabbits against scarlet fever streptococci. The case was parallel to the time, in 1894, when diphtheria serum was first introduced. In the hands of many people it was a failure, but in some hospitals it produced dramatic effects. The explanation was that the serum available in this country was a very low-grade serum. It cured some cases, but it did not contain enough antitoxin to be generally convincing.

With regard to the bacteriology of this disease, Gordon, of Chicago, had recently reported that of 100 scarlet fever cases, sixty-two among the control group who had not been treated with serum, and thirty-one who had been so treated, had the hæmolytic streptococcus of scarlet fever in the throat on the twenty-eighth day. Scarlet fever patients had apparently been discharged from hospitals with hæmolytic streptococci in their throats for years past, but they were not acutely infectious, or " return " cases would more often occur.

With regard to Dr. Martin's question, military records showed that there had been epidemics of sore throat without a rash in groups of soldiers confined to barracks, and that these had spread over large groups of men. One such had occurred in the South African war.

Reverting to the old work on this subject, Dr. Gabritchewsky's death, in 1905, was to be regretted. It was most refreshing to read his work and to note the logical way in which he passed from one step to another. He had produced a highly successful anti-scarlet fever vaccine.

With regard to the cases mentioned by Dr. Parish, the septic element of scarlet fever was the important one. The deeper one went into it the more difficult it became, and the more clearly it was seen that fascinating problems lay ahead. Possibly there was an overlapping in, or even identity of, the antigens of all the hæmolytic streptococci, but the baffling thing to-day was the occurrence of later septic phenomena. In the rabbits experimented upon, the first attack of the streptococcus was neutralized by the serum, and the protected rabbits were alive and well after the control rabbits were dead, but later joint lesions had developed. This

curious paradox was first recorded, in connexion with pneumonia, by Mair and Gaskell. One could immunize a rabbit with dead pneumococci at first, then with the living pneumococci, and the rabbit's serum would protect a mouse against many lethal doses of pneumococcus ; endocarditis and other pneumococcal lesions developed in the rabbit itself. Until a means of preventing this late arthritis in the rabbits was discovered, it would not be possible to avoid these serious complications. Dochez had sent to him (the speaker) some of his antibacterial serum, and he had tried that and other sera supposed to be antibacterial and containing a large amount of agglutinin, but those sera had not saved the rabbits from this late arthritis. The worker who could solve the problem of preventing these complications would earn a great debt of gratitude.



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